Watchful waiting in aortic stenosis: are we ready for individualizing the risk assessment?

João L. Cavalcante*

UPMC Heart & Vascular Institute, Advanced Cardiovascular Imaging, University of Pittsburgh, Pittsburgh, PA, USA

Online publish-ahead-of-print 3 November 2015

This editorial refers to ‘A clinical risk score of myocardial fibrosis predicts adverse outcomes in aortic stenosis’, by C.W. Chin et al., on page 713.

With the aging of the population and increased use of echocardiography, aortic stenosis (AS) has become one of the most common valvulopathies encountered in the general population. Current guidelines advocate aortic valve replacement (AVR) for severe AS patients in the presence of either: (i) classical symptoms (angina, syncope, or exertional dyspnoea) often difficult to ascertain in these patients with several co-morbidities; and/or (ii) left ventricular (LV) systolic dysfunction (i.e. LV ejection fraction <50%) which could be permanent. While for symptomatic patients with severe AS the decision to treat is relatively simple, the timing for prophylactic intervention in an asymptomatic patient with preserved LV systolic function remains controversial and a matter of continuous debate.

Should we then focus on the asymptomatic patients? For these patients, the two main concerns are the small risk of sudden cardiac death (∼1%/year) and the potential development of subclinical LV dysfunction. The current guidelines emphasize the role of objective assessment of functional capacity and symptomatic status with supervised exercise testing, which, although important, might not be feasible in some patients. In the absence of unmasked symptoms and/or markers of increased risk such as hypotension and/or failure of blood pressure to increase with exercise, the approach of watchful waiting with close surveillance for symptoms development seems reasonable. However, there is a marked heterogeneity, with subsets of patients at higher risk for development of symptoms and/or LV dysfunction that could potentially benefit from early AVR provided there is low surgical risk. Those would include asymptomatic patients with high peak aortic valve jet velocity >5.0 m/s² or >5.5 m/s in the European guidelines (Class IIa) which also considered important for decision ‘marked elevation of BNP on repeated measurements, mean AV gradient increase >20 mmHg with exercise, and excessive LV hypertrophy in the absence of hypertension’ (Class IIb).

What could be the main drivers increasing the asymptomatic patient’s vulnerability? The progressive valvular and arterial pressure overload produces several adaptive compensatory changes aiming to decrease LV wall stress. The resulting LV hypertrophy comes at a cost given its association with progressive myocardial fibrosis and stiffness which clinically translates into increased risk for adverse cardiovascular events and potential for LV dysfunction. The transition from compensatory adaptive hypertrophy to LV decompensation appears to be largely driven by two main processes: myocyte cell death (apoptosis) expressed by the release of troponin I, and myocardial fibrosis which can be detected non-invasively by cardiac magnetic resonance imaging (CMR) (Figure 1). Importantly, the variability of the disease progression and subsequent myocardial hypertrophic response is quite heterogeneous and not entirely explained by the haemodynamics, offering the opportunity to individualize the risk stratification among asymptomatic patients with AS.

Over the last 6 years, CMR has provided new insights into the risk stratification of patients with severe AS. Using late-gadolinium enhancement imaging, several groups have found that the presence of replacement midwall myocardial fibrosis (MWF) predicts worse outcomes (all-cause and cardiovascular mortality) over and above traditional predictors such as age, LV ejection fraction, and echocardiographic measures of AS severity. Interestingly, despite the protective benefits of AVR, patients with MWF who undergo AVR are still at higher risk than those without MWF. Thus, MWF appears to be an early marker of LV decompensation, and its presence identifies a phenotype of patients at higher risk for decompensation in which prophylactic AVR should be considered.

There is no doubt that CMR is an excellent non-invasive imaging tool; however, its availability, patient/device-specific contraindications, and required technical expertise limit its wide clinical applicability. In the current cost-saving medical care environment, it would be valuable to identify potential surrogates of MWF, which could indirectly help in identifying potentially vulnerable patients at increased risk of LV decompensation.

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

1 doi:10.1093/eurheartj/ehv578
2 Corresponding author. UPMC Heart & Vascular Institute, Advanced Cardiovascular Imaging, University of Pittsburgh, Pittsburgh, PA, USA. Tel. +1 412 648 6598, Fax: +1 412 648 6101, Email: cavalcantejl@upmc.edu

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2015. For permissions please email: journals.permissions@oup.com.
In this study of Chin et al., the authors build on their previous work proposing a scoring system to identify high-risk patients that would have the CMR phenotypic expression of MWF. In the initial derivation cohort, MWF was associated, as expected, with more advanced AS severity, hypertrophic LV remodelling, and worse diastolic and longitudinal functions. The derived scoring system included known clinical (age, gender) and echocardiographic characteristics (peak AV velocity), but also troponin I (a very sensitive marker of myocardial cell death) and LV strain pattern on ECG (a very specific marker of LV hypertrophy). This scoring system was then further validated using two independent cohorts of patients with moderate to severe AS. The primary outcome was a combined endpoint of cardiovascular mortality, congestive heart failure, and new symptoms of angina, syncope, or dyspnoea. Importantly, this new clinical scoring system identified a subset of low-risk patients at a lower event rate (3.9 events/100 patient years) vs. high-risk patients (30.1 events/100 patient years). Furthermore, it seems that troponin I might be a better risk-stratifying marker associated with earlier MWF changes than brain natriuretic peptide (BNP) or N-terminal pro brain natriuretic peptide (NT-proBNP), not only due to the differences in the assays used but also the lack of specific thresholds.

Before we consider adopting this handy scoring system, it would be important to highlight some potential challenges we still have resolving this problem. First, nearly one-third of the patients in the derivation cohort had symptomatic severe AS for whom the decision to proceed with AVR should have occurred without much hesitation. Secondly, data regarding the objective assessment of a patient’s functional capacity using a simple 6-min walk test and/or formal exercise testing could have added important prognostic value and helped in the decision-making process of these patients. Thirdly, inherent to their study design, MWF was not confirmed in their validation cohorts by CMR imaging. Furthermore, myocardial strain analysis could have added further insights into the risk stratification of this cohort of asymptomatic AS patients all with preserved LV systolic function. Nonetheless, the authors are to be acknowledged for their study methodology, with stringent thresholds to define low- and high-risk groups, and for externally validating the proposed scoring system into two separate and independent cohorts, adding statistical merit and clinical relevance to their work.

Although focal MWF is an important marker in AS, diffuse myocardial fibrosis appears to be more prevalent according to histological data. Recent technological advances in CMR imaging with the use of T1 mapping and extracellular volume fraction now allow for a non-invasive ‘imaging biopsy’ and precise quantification of diffuse myocardial fibrosis. These imaging biomarkers have been shown to be elevated in patients with severe AS vs. younger healthy controls. However, when asymptomatic patients with severe AS were compared with age-matched controls, significant overlap between the two groups was seen. Therefore, at the present time, we are not able to distinguish sufficiently and/or guide treatment decisions on an individual patient basis using solely these parameters. It remains to be determined whether identification and quantification of focal or diffuse myocardial fibrosis by CMR pre- and post-intervention can provide incremental prognostic value for severe AS patients treated with either surgical or transcatheter AVR. Several ongoing studies are investigating and comparing different CMR methods of non-invasive quantification of myocardial fibrosis.
fibrosis in AS patients. These results will be important to determine the prognostic significance of these promising imaging biomarkers over and above traditional risk assessment.

In the absence of previous (and possibly future) randomized controlled trials comparing early surgery vs. watchful waiting in asymptomatic patients with severe AS, we will continue to rely on our best clinical judgement using a case-by-case basis. This important work by Chin and colleagues\(^{11}\) provide us with the framework over and above traditional risk assessment.

Asymptomatic patients with severe AS, we will continue to rely on controlled trials comparing early surgery vs. watchful waiting in over and above traditional risk assessment.

The prognostic significance of these promising imaging biomarkers could potentially derive benefit from early AVR before LV decompression occurs.

**Conflict of interest:** J.L.C. has received investigator-initiated research grant support from Medtronic Inc.

**References**

5. Shah PK. Should severe aortic stenosis be operated on before symptom onset? Severe aortic stenosis should not be operated on before symptom onset. *Circulation* 2012;126:118–125.